Abuse-Deterrent Opioids – Evidence Evaluation & Labeling

Medication: Arymo ER®

Evaluation Date: 05/18/17 Evaluation History: ☒ Initial Version 1.0, or ☐ Version _____

Current Product Labeling established: ☐ Prior to or ☒ After publication of FDA Guidance to Industry Document (4/2015)

This is a: (Check all that apply)

- ☒ New product
- ☐ Existing product, new formulation
- ☐ Existing product with new/updated labeling
- ☐ Other: _____

Product Abuse Deterrent Property Classification: – Check all that apply

- ☒ Physical / Chemical barrier
- ☐ Agonist / Antagonist combination
- ☐ Aversion
- ☐ Delivery System
- ☐ New Molecular entity or Prodrug
- ☐ Combination (check combined items)
- ☐ Novel Approach

Product Labeling:

Does the product have FDA abuse deterrent labeling? ☒ Yes or ☐ No Year obtained: 2017

Abuse Deterrent Evidence provided. Summary of in-depth literature review and product evaluation based on FDA Guidance to Industry Document

☒ Laboratory-based in vitro manipulation and extraction studies (Category 1)

Description of Research: *In vitro* manipulation and extraction data indicates tablets resist manipulation using most household tools, particle size reduction is difficult, a viscous gel is formed when subjected to liquid, the gel that is formed generally resists passage through a needle, extraction in large volumes of liquid takes extended periods of time, free-base morphine cannot readily be extracted and smoking is not a viable method of abuse.

☒ Pharmacokinetic Studies (Category 2)

Description of Research: Pharmacokinetic studies reveal that manipulation of Arymo ER® results in a shorter time to peak concentration (T_{max}) by a mean of approximately 1.1 hours, the mean exposure (AUC) to morphine is slightly lower with manipulated compared to intact tablets, and the peak plasma concentration (C_{max}) is slightly increased with manipulated tablets compared to intact (19.0 [9.6] ng/mL versus 17.2 [4.3] ng/mL, respectively).

☒ Clinical Abuse potential studies (Category 3)

Description of Research: Oral clinical abuse potential study assessed peak effect for drug liking on VAS of manipulated Arymo ER® compared to morphine ER tablet (generic MS Contin®) as the primary endpoint. Peak drug liking was significantly lower for manipulated Arymo ER® compared to manipulated morphine ER (P=0.007).

☒ Clinical Abuse potential studies (Category 3)

Description of Research: Intranasal clinical abuse potential study assessed peak effect for drug liking on VAS of manipulated high volume and low volume Arymo ER® intranasally and intact Arymo ER® orally compared to morphine ER tablet (generic MS Contin®) intranasally. Peak drug liking for manipulated high and low volume Arymo ER® intranasally and intact Arymo ER® was significantly lower compared to manipulated morphine ER intranasally (P<0.0001 for all comparisons).

☐ Additional Studies / Post Market data which assessed the impact of abuse-deterrent formulation (Category 4)

☐ Post market

☐ Formal studies included recommended study design features (see page 19 FDA Guidance document)

Description of Research: _____

_____

☐ Determination if use of product results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death

Description of Research: _____

_____

☒ Outcome Measures and Data Interpretation in Abuse Potential Studies

- Standardized Instruments

☒ Visual Analogue Scales (VAS)

Description of Research: Drug liking, take drug again, Drug Effects Questionnaire, ease of snorting

☐ Profile of Mood States

Description of Research: _____

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- Data Interpretation

☒ Primary Analysis

Description of Research: Comparison of median peak drug liking VAS scores (both studies)

☒ Statistical Analysis

Description of Research: Provided descriptive statistics (both studies); both studies followed FDA guidance to industry on statistical analysis for abuse-deterrence studies based upon comparison of median drug liking VAS (acceptable per FDA when nonparametric method necessary); analyzed using a linear mixed-effects model with fixed effects for sequence, period, and treatment, and random effect for participant nested in sequence (both studies)

☒ Data and dropout for non-completers

Description of Research: Data regarding dropout and non-completers accounted for (both studies)

☐ None of the above

Strength of Evidence of Abuse Deterrent Properties:

☐ Evidence is based on physical/chemical property, theoretical assumptions or manufacturer's claims and is not yet supported by scientifically sound outcome data which demonstrates a reduction in the abuse of the product in the community setting compared to levels of abuse, overdose, and death that occurred when only formulations of the same opioid without abuse-deterrent properties were available (Category III)

☒ Evidence is based on physical/chemical property, clinical abuse potential studies or laboratory manipulation studies and is not yet supported by scientifically sound outcome data which demonstrates a reduction in the abuse of the product in the community setting compared to levels of abuse, overdose, and death that occurred when only formulations of the same opioid without-abuse-deterrent properties were available (Category II)

☐ There is evidence, supported by scientifically sound outcome data, which demonstrates a reduction in the abuse of the product in the community setting compared to levels of abuse, overdose, and death that occurred when only formulations of the same opioid without abuse-deterrent properties were available (Category I)